--20. The bovine growth hormone of claim 19 which comprises the amino acid sequence at positions 2-191 of Figure 1.

C 3

21. The bovine growth hormone of claim 19 wherein the cells are *E. coli*.

22. The bovine growth hormone of claim 19 which is in purified and isolated form.--

REMARKS

Claim 19 has been amended to overcome the objection by rewriting it to include all of the limitations of the canceled claim 18 from which it originally depended. The additional claims 20-22 are supported by the claims as originally filed (see claim 13), by Figure 1 as included in the original application, and on page 10 of the specification, first full paragraph. No new matter has been added and entry of the amendment is respectfully requested.

The sole basis for rejection is made under 35 U.S.C. § 102(b)/103 over Daniels (U.S. Patent No. 3,265,579) which describes the purification of bovine growth hormone, ultimately from bovine pituitaries. The Office takes the position that the claimed bovine growth hormone (bGH) is either inherently exactly the same inherently as that purified from bovine pituitaries, or that the differences from that of Daniels represent an obvious variation. In the view taken by the Office, minor variations which do not alter the activity or function of the protein do not render the claimed protein patentable. The Office is correct that it is the nature of the product as compared to the product disclosed in the art which determines patentability, and that the novelty of a process *per se*, if it yields an obvious or anticipated product, will not confer patentability on claims directed to the product.

However, it is applicants' position that the claimed bovine growth hormone is materially different from the bGH described by Daniels. The difference does not lie in the degree of purity

or the glycosylation pattern, but rather in the most relevant feature possible, the ultimate safety of the product.

Specifically, absent the recombinant production of bovine growth hormone as required by the present claim, the product, bovine growth hormone prepared as in Daniels, carries the very real risk of causing the infection of animals to which it might be administered with bovine spongiform encephalopathy (BSE), commonly known as mad cow disease. There is, at present, no possible way to guarantee that bovine growth hormone prepared, as that of Daniels has been prepared, from bovine pituitaries, would be free of this infective agent. The prevalence of BSE in European stocks is by now well understood, and there can be no assurance that it is not present in animals from other origins. The enclosed article from *Nature* (1996) 382:4 indicates the prevalence of BSE in Europe, and also states that the most infective parts of the animal are the brain and the spinal cord. Of course, the pituitary is associated with the brain. The problem is sufficiently serious that the French Primer Minister recommended a total ban on the use of all central nervous system tissues of ruminants for human consumption, even on animals born after August 1991, subsequent to a change in feeding patterns for European cattle. The Advisory Board charged with this problem specifically advised the government to act as if BSE could be transmitted to humans. (*Ibid.*, p. 5).

In the event that the Office considers this simply a minimal risk, and thus imparting no patentable distinction to the recombinant product, applicants ask that it be remembered that in response to the recognition of this problem, wholesale slaughter of British cattle was considered.

The clear importance of this risk factor is also evident from the history of human growth hormone, because it is clear that BSE and Creutzfeldt-Jakob disease (CJD), which affects humans, are completely similar in that they are caused by an abnormal form of the prion protein. (See Prusiner, S.B. *Science* (1991) 252:1515.) Thus, the significance of the possible contamination of bovine growth hormone with the infective agent for BSE is comparable to the history of the contamination of human growth hormone obtained from pituitaries contaminated

with the agent for CJD. It may be recalled that in 1985, deaths attributed to CJD resulted in a complete halt to the distribution of human growth hormone and other pituitary products monitored and managed by the National Institutes of Health. Only the availability of the recombinant form of human growth hormone made possible the continued treatment of persons who had been recipients of the pituitary-derived material. This is documented, for example, in *Science* (1985) 228:1176-1177 and in an article by Brown, P. *et al. New England Journal of Medicine* (1985) 728-738. As further stated in this article on page 729, the CJD "virus" resists treatment with chemicals such as acetone, ether, alcohols, iodine, hydrochloric acid and formaldehyde and even 15-minute exposures to sodium hypochlorite, sodium hydroxide and steam autoclaving. As stated at page 79, right-hand column, "It seems prudent to suppose that although nearly total inactivation of virus may occur, no amount of processing can be guaranteed to result in a fully sterile end product."

Indeed, NIH publication No. 88-2793 published in December of 1987, which provides a summary of this entire situation, states on page 3 that

> While the methods of preparation of pituitary hGH used since 1977 yield a product that is more than 95% pure, there is no certainty that the modern preparation is safer than the hormone extracted before 1977.

and concludes,

> Extraction methods that result in 95% chemical purity still may not remove or inactivate the CJD agent.

A more recent article by Hintz, R.L. *J Clin Endocrinol Atab* (1995) 80:2298-2301 confirms that since 1984, 15 definite cases of CJD associated with the use of human growth hormone obtained from pituitaries had been documented in the United States and that a total of at least 60 cases have occurred worldwide.

If the PTO does not take this risk seriously, the NIH clearly does. In addition to halting the supply of pituitary-derived hGH altogether, the NIH followed up with informative letters to

both practitioners and growth hormone recipients apprising them of the investigations concerning the risk that people who may have been administered the pituitary-derived form (the NHPT growth hormone) might continue to be under. At least two such letters were sent to practitioners, one dated 28 October 1987 and a second dated 10 January 1994. The 1987 letter indicated that the risk was considered sufficiently serious that blood banking organizations had jointly decided to exclude pituitary growth hormone recipients from being blood donors. (See the end of the first paragraph.) At least two letters were sent to growth hormone recipients, one in February of 1991 and another in January of 1994.

The enclosures thus indicate the following: while from a structural and composition standpoint, a BSE infective agent would, even if present, constitute a vanishingly small percentage of the bGH prepared from bovine pituitaries as disclosed in the prior art, its importance cannot be measured by this criterion. In view of the current concern over the prevalence of BSE in Europe, is it even imaginable that any government would permit the use of pituitary-derived bGH in animals intended for human consumption or milk production?

Similarly, while the CJD particles associated with pituitary-derived human growth hormone also constituted a vanishingly small percentage of the hGH compositions, their presence resulted in at least 75 deaths, in the complete stoppage of distribution of the pituitary-derived hormone, and in the substitution therefor of the recombinantly-produced growth hormone analogous to that claimed.

Not only was distribution of pituitary human growth hormone halted, the NIH has continued to study the problem and to inform practitioners and recipients. Of particular interest, perhaps, is the information in the letter mailed October 28, 1987 by the NIH to practitioners describing what NIH was doing in connection with this putatively minor contaminant in human growth hormone preparations. As stated on page 2 of the letter, samples of all available batches of growth hormone distributed through the NHPP were inoculated intracerebrally into primates. It was intended to follow these animals for at least five years. Furthermore, the NIH stated that it

was conducting an epidemiologic follow-up of all NHPP growth hormone recipients which amounted to approximately 10,000 children. Clearly, the NIH did not consider that the pituitary-derived human growth hormone containing a minor compositional variant the mere possibility of contamination with CJD was inconsequentially different from recombinantly-produced human growth hormone. Neither does the claimed recombinantly produced bovine growth hormone, which is clearly absolutely free of BSE, lack any significant functional distinction from the pituitary-derived bGH of the prior art. The difference is that one is a useful product and the other is not. To conclude that this is a patentable distinction is, if anything, an understatement of its importance.

In view of the foregoing, it is believed that claims 19-22 are clearly patentable over the art and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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